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(57) Abstract

A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising: a) at least one blister card, wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into sections separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time in which the dose is to be administered; b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and d) a reminder aid. The present invention further relates to a method of aiding and/or improving patient compliance for complex peroral drug regimens by the use of an effective compliance packaging. Especially preferred are compliance packages and methods relating to the treatment of *H. pylori* mediated upper gastrointestinal disorders or infections.

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COMPLIANCE PACKAGE AND METHOD OF IMPROVING OR AIDING PATIENT COMPLIANCE FOR COMPLEX DRUG REGIMENS

BACKGROUND OF THE INVENTION

The present invention relates to a pharmaceutical package for aiding or increasing patient compliance for the administration of peroral complex pharmaceutical drug regimens. Further, the present invention relates to a method of aiding and/or improving patient compliance for complex peroral drug regimens by the use of an effective compliance packaging.

Patient compliance has been defined as "the extent to which an individual's behavior coincides with medical or health advise. Compliance with therapy implies a positive behavior in which the patient is motivated sufficiently to adhere to the prescribed treatment because of a perceived self-benefit and a positive outcome (e.g. enhanced daily functioning and well-being." *Remington's Pharmaceutical Sciences,* Chpt. 103, Vol. II, p. 1796 (19th Ed.1995).

Most physicians assume that, when they a diagnosis a condition and select a therapeutic agent and regimen for a patient to treat that condition, the patient will follow their recommendation and take the therapeutic agent according to instructions. However, patient compliance studies indicate otherwise. Studies indicate a high incidence of medication errors and non-compliance with respect to taking prescription drugs. Stewart, R. B., and Cluff, L.E. A review of medication errors and compliance in ambulant patients. *Clin Pharm Ther,* 1972, 13, 463-468.

In fact the problem of non-compliance can increase health-care costs. For example, it is estimated that over 50% of patients taking antihypertensive medication are non-compliant and/or stop taking their medications within the first 12 months of treatment. Each year, thousands of deaths and hospital admissions result from over or undermedicating. In addition about 25% of nursing home admissions are a result of the patient's inability to take his or her medications correctly. This can result in added costs for additional prescriptions, additional physician visits, hospitalization for consequences of untreated diseases or rehabilitation cost and/or home health care costs for untreated or undertreated diseases. Of course, the consequence of non-compliance with antihypertensives can be life threatening, and can result in strokes, myocardial infarction, etc. Eraker, S.A., et al., Understanding and Improving Patient Compliance, *Ann Intern Med,* 100, 258 (1984). Forcinio, H. Packaging Solutions That Help Patient Compliance, *Pharmaceutical Technology*, March 1993, p. 44-50.

Increased health care cost is also associated with antimicrobial therapy non-compliance. In particular, non-compliance with antimicrobial treatment can increase cost due to the need to prescribe additional medications to retreat the infection, additional lab work to re-diagnose the infection, etc. Moreover, antimicrobial non-compliance can also contribute to the development of resistance.

Non-compliance encompasses a variety of behaviors. Acts of omission include drug underuse. For example the patient may take less medicine or take it less frequently than prescribed and may even take drug "holidays." The patient may not obtain the initial or a refill prescription, or may stop taking the medication too soon. Acts of commission include drug overuse, taking too high a dose or taking a dose too frequently. They also include taking too low a dose such as skipping a dose. The patient may even share medication with family members or knowingly consume a food, beverage, or other drug that can interact with one's prescription drug. Prescription Medicine Compliance: A Review of the Baseline of Knowledge, NCPIE Report, Aug. 1995

Numerous factors determine the probability for compliance and explain why patients do not comply with prescribed drug therapy. One factor is the type of illness involved. For example, patients having chronic illness or illnesses that are not associated with significant symptomatology, such as hypertension and hypercholesterolemia, are likely to display higher medication non-compliance rates. It is somewhat understandable for patients to become discouraged with extended therapeutic drug regimens that do not eventually "cure" the disease. However, one can expect that compliance will increase where increased disability results from non-compliance.

Another reason that many patients stop taking prescribed medication too soon, involves the disappearance of symptoms. In particular patients who are prescribed antibiotics often stop taking the antibiotic on the fourth day of treatment. It is at this point that the symptoms start to disappear and the patient feels better. This problem may even be further compounded where the antibiotic treatment involves the administration of more than one antibiotic agent. An example of this type of regimen is triple-therapy regimen for the treatment of *H. pylori* infections, consisting of: (1) a bismuth salt (e.g., bismuth subsalicylate), (2) metronidazole and (3) amoxicillin or tetracycline. Mohler, D.N. et al., Studies in the Home Treatment of Streptococcal Disease, I. Failure of Patients to Take Penicillin as Prescribed, *New Engl J Med,* 252, 1116 (1955). Mattar, M.E. et al., Pharmaceutic Factors Affecting Pediatric Compliance, *Pediatrics,* 55, 101 (1975). U.S. Pat. No. 5,256,684, Marshall, issued October 26, 1993, The Procter & Gamble Company.

In addition, other factors, related to non-compliance, include the age of the patient. Non-compliance with the elderly population is generally higher than other groups. This can be attributed to a variety of factors such as declining mental functioning, increasing

numbers of medication prescribed and the increase in side effects and/or drug interactions associated with these multiple drug regimens. Also, improper dosing leading to side effects may also contribute to non-compliance. In addition non-compliance among the elderly is associated with taking more than five prescription medications concurrently, an inability to read prescription labels and difficulty opening flip-off type medication container lids. Murray, M.D. et al., *DICP* 20:146 (1986.)

The physician's and pharmacist's relationship with the patient will influence medication compliance. For example, how clearly the physician and/or pharmacist explains the treatment regimen to the patient being treated will influence how likely the patient will comply with the drug therapy prescribed.

Multiple medication administration, complex treatment regimens, frequent dose regimens and the physical characteristics of the dosage form (tablet v. capsule v. liquid), can contribute to non-compliance. Studies have reported that non-compliance increases when the number of tablets or capsules taken daily increases from one to four times daily. Gatley, M.S. To be taken as directed. *Jl R Coll Gen Pract*, 1968, 16, 39-44. Eisen, S.A. et al., *Arch Intern Med* 150, p. 1881, 1990. "The administration of medication at frequent intervals makes it more likely that the patient's normal routine or work schedule will have to be interrupted to take a dose of medication and in many cases the patient will forget, not want to be inconvenienced or be embarrassed to do so." *Remington's Pharmaceutical Sciences*, Chpt. 103, Vol. II, p. 1800 (19th Ed.1995).

A specific example of a complex treatment regimen includes the treatment for *H. pylori* mediated upper gastrointestinal disorders or infections. Currently, single agent antimicrobial approaches designed to eradicate infection by *H. pylori* provide unacceptable eradication rates (i.e., < 80%). As a result, treatment comprises the administration of more than one therapeutic agent. Examples of such combination therapy include the administration of 1) at least one antimicrobial agent(s) used in combination with a proton pump inhibitor; and 2) at least one antimicrobial agent(s) used in combination with bismuth or a bismuth salt. An example of a particularly preferred combination includes a triple-therapy regimen consisting of: (1) a bismuth salt (e.g., bismuth subsalicylate), (2) metronidazole and (3) amoxicillin or tetracycline. These types of treatment regimens, due to their complexity, are particularly vulnerable to patient non-compliance.

A number of strategies have been proposed and developed to enhance medication compliance by patients. In addition to oral and written communication/counseling of patients by the physician and/or the pharmacist, audiovisual materials and improvement in the patient/physician or pharmacist relationship may enhance patient compliance.

Moreover, medication compliance aids have been developed to enhance compliance. One example is a compliance package. A compliance package is defined as

"a prepackaged unit that provides one treatment cycle of the medication to the patient in a ready-to-use package." *Remington's Pharmaceutical Sciences,* Chpt. 103, Vol. II, p. 1804 (19th Ed.1995). D.L. Smith, Compliance Packaging: A Patient Education Tool, *Amer Pharm,* Vol. NS29, No. 2, p. 42-53,1989.

Packages for oral contraceptives were possibly the first packaging of this type to be introduced and continue to be used extensively for these agents. Specific examples of oral contraceptive compliance packaging are listed in the *Physicians' Desk Reference*, p. 306, 322, 323, 49 ed. 1995.

For example, Ovcon® 35 and 50 (Bristol-Meyers Squibb), Ortho-Novum® Dialpak 1/35, 1/50, 10/11 and 7/7/7 (Ortho Pharmaceutical Corp.), Loestrin® Fe 1/20 and 1.5/30 (Parke-Davis), etc. are oral contraceptives packaged in blister cards. These packages are generally a single blister card, with 21 or 28 day regimens. Each tablet is labeled with a particular day of the week so that the patient can tell if any doses have been missed. Written patient information, which informs the patient of risks and benefits of therapy, is a mandatory requirement for oral-contraceptive packaging.

Additional examples of compliance packaging include Rheumatrex® Dose Packs made by Lederle Laboratories, containing four blister-pack cards each containing either 2, 3, 4, 5, or 6 tablets (for 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per week, respectively) for 1-week's therapy of methotrexate.

Medrol® Dosepak (Upjohn Company), is a packaging designed for the administration of steroids, (i.e. methylprednisolone) which require staggered dosing. For each day of drug treatment the number of tablets (and total dose) that the patient must take, decreases. For example, the Medrol Dosepak contains 21, 4mg tablets for 6 days of treatment where for each day of treatment, the total daily dose decreases by one tablet.

Axid® Convenience Pak previously made by Eli Lilly & Company, which contained a 30-day supply of nizatidine in a single medication blister card, is another example. This medication is to be taken once a day and is for the treatment of duodenal ulcers.

Zithromax® Z-Pak made by Pfizer Laboratories, contains a single medication blister card with 6, 250mg capsules. Each blister medication card is labeled with "Day 1 to Day 5" for each dose, the first dose being two, 250 mg capsules labeled "Day 1." Each subsequent capsule is labeled with "Day 2" to "Day 5."

A further example of a compliance package includes "MacPac®" made by Norwich Eaton. Although no longer available on the market, this package contained an information booklet and seven blister-pack cards each card containing a daily dose (i.e. four capsules) of Macrodantin (nitrofurantoin macrocrystals.) Each dose (capsule) was labeled "Breakfast," "Lunch," "Dinner," and "Bedtime." The MacPac also contained two stickers

for the pharmacist to apply to the package upon dispensing. These stickers contained the information: "Take with food or milk" and "Complete the full time of treatment prescribed by your physician." Furthermore, this package contained a reminder card between the third and forth medication cards, i.e between the third and forth day of treatment.

Despite the development of the above types of compliance packaging, additional improvements are needed to further enhance patient compliance, especially for complex peroral drug regimens. Further improvements are needed in order to ensure that the patients understand drug information provided in compliance packaging and to ensure that they are sufficiently motivated, through compliance packaging to complete a full course of drug treatment.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) at least one blister card,

wherein each blister card comprises the total daily dose of the peroral complex drug regimen; wherein the blister card is divided into sections, preferably perforated sections, separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time the dose is to be administered; and wherein preferably each blister card comprises an indicia denoting each separate day of treatment;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) preferably a reminder aid selected from the group consisting of:

1) one or more reminder cards comprising information to remind the patient when to take a dose of the complex drug regimen;

2) one or more adhesive stickers comprising information to remind the patient when to take a dose of the complex drug regimen;

3) a case of the size to contain a single blister card, the case comprising an alarm which can be set by the patient to sound at the time that the next dose is to be administered; and

4) combinations thereof.

Preferably the complex drug regimen comprises varying the dosage level or the dosage interval for a single therapeutic agent, the simultaneous administration of more than one therapeutic agent, or the concurrent administration of more than one therapeutic agent.

It is understood that all of the above listed elements of the compliance package of the present invention are housed in a container made of any suitable material. Preferably the container is made of any suitable paper and/or plastic material.

Preferably the blister package is child resistant and "senior friendly."

Also, preferably the blister cards are separated, at approximately one-fourth to three-fourths of the way between the start and the finish of the complex drug regimen, by a card comprising patient information and patient incentive information. This card preferably contains a statement on the importance of completing the full course of drug therapy to avoid disease or symptom reoccurrence.

Preferably the compliance package comprises a number of reminder cards or adhesive stickers equal to the number of daily doses to be administered by the patient. Preferably the reminder aid is one or more adhesive stickers.

Preferably each reminder aid (adhesive stickers or reminder card) is provided in a form to allow the patient to place the sticker or card at a location that the patient will be, at the time a dose of the complex drug regimen is due to be taken by the patient.

Further, the present invention relates to a method of aiding and/or improving patient compliance for complex peroral drug regimens by the use of an effective compliance packaging.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical package for aiding or increasing patient compliance. In particular the present invention reduces the risk of omission of doses, dosage errors (amount of individual dose), drug administration errors, errors in the time of administration and/or premature discontinuation, for peroral complex drug regimens. Specifically the present invention relates to a pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) at least one blister card,

wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into sections, preferably perforated sections, separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time the dose is to be administered; and wherein preferably each blister card comprises an indicia denoting each separate day of treatment;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) preferably a reminder aid selected from the group consisting of:

1) one or more reminder cards comprising information to remind the patient when to take a dose of the complex drug regimen;

2) one or more adhesive stickers comprising information to remind the patient when to take a dose of the complex drug regimen;

3) a case of the size to contain a single blister card, the case comprising an alarm which can be set by the patient to sound at the time that the next dose is to be administered; and

4) combinations thereof;

wherein preferably the complex drug regimen comprises varying the dosage level or the dosage interval for a single therapeutic agent, the simultaneous administration of more than one therapeutic agent, or the concurrent administration of more than one therapeutic agent.

It is understood that all of the above listed elements of the compliance package of the present invention are housed in a container made of any suitable material. Preferably the container is made of any suitable paper and/or plastic material. Also, this container is preferably of square or rectangular dimensions. Preferably the outer container for the above listed components is of a size and dimension to accommodate standard pharmacy prescription labels.

Preferably the blister package is child resistant and senior friendly.

Also, preferably the blister cards are separated, at approximately one-fourth to three-fourths of the way between the start and the finish of the complex drug regimen, by a card comprising patient information (side effect, dosing, and/or disease information) and

patient incentive information. This card preferably contains a statement on the importance of completing the full course of drug therapy to avoid disease or symptom reoccurrence.

The methods and packages of the present invention comprise a safe and effective amount of one or more therapeutically active agent(s). The phrase "safe and effective amount," as used herein, means an amount of therapeutically active agent high enough to provide a significant positive modification of the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of therapeutically active agents will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific therapeutic agent selected, and like factors.

As used herein "administering" refers to any method which, in sound medical practice, delivers the therapeutically active agents or compositions containing the therapeutically active agents, used in the compliance package of the present invention, to the patient to be treated in such a manner to be effective in the treatment of the disorder.

As used herein the term "therapeutic agent" includes any pharmaceutical agent useful for the treatment of a disease or condition, to alleviate symptoms, etc.

The term "peroral complex drug regimen" includes any peroral drug regimen which requires the administration by the patient being treated, of:

1. Varying dosage regimens for a single therapeutic agent (i.e. where the dose of a single therapeutic agent is varied over the course of the drug treatment or where the intervals between dosage administration for a single therapeutic agent is varied over the course of the drug treatment.)

2. The administration of more than one therapeutic agent simultaneously. As used herein the term "simultaneous" means that the two or more therapeutic agents are given at the same time, beginning and ending on the same day.

3. The administration of more than one therapeutic agent concurrently. The term "concurrently" as used herein means that the administration of two or more therapeutic agents are overlapping.

4. The administration of more than one therapeutically active agent consecutively. The term "consecutively" herein means that the administration of two or more therapeutic agents are sequential, but substantially continuous, i.e. the administration of two or more agents is separated by no more than about 24 to 48 hours.

Specific examples of peroral complex drug regimens include those described in U.S. Pat. No. 5,256,684, Marshall, issued October 26, 1993, The Procter & Gamble Company, which describes a method for the treatment of humans and lower animal patients having a gastrointestinal disorder associated with *H. pylori*, comprising administering

bismuth and at least one antimicrobial, the administration being simultaneous, concurrent or consecutive. The Marshall reference is incorporated herein by reference in its entirety.

Particularly preferred peroral complex drug regimens include those for the treatment of *H. pylori* mediated upper gastrointestinal disorders or infections. In particular, such gastrointestinal disorders are those affecting the upper-gastrointestinal tract, and those mediated by *H. pylori* (herein referred to as "*H. pylori*-mediated gastrointestinal disorder(s)." Such gastrointestinal disorders include, for example: *H. pylori* -mediated disorders not manifested by presence of ulcerations in the gastric mucosa (herein "non-ulcerative gastrointestinal disorder"), including chronic or atrophic gastritis, non-ulcer dyspepsia, esophogeal reflux disease and gastric motility disorders; and "peptic ulcer disease", i.e., gastric, duodenal and jejunal ulcers. *H. pylori* treatment comprises the administration of more than one therapeutic agent. Examples of such combination therapy include the administration of 1) at least one antimicrobial agent(s) used in combination with a proton pump inhibitor and 2) at least one antimicrobial agent(s) used in combination with bismuth or a bismuth salt.

Proton pump inhibitors include, but are not limited to omeprazole (known under the tradename of Prilosec® available from Astra Merck), lansoprazole (known under the tradename of Prevacid® available from TAP Pharm), pantoprazole, and mixtures thereof.

Bismuth salts include, but are not limited to, bismuth aluminate, bismuth citrate, bismuth subcitrate, bismuth nitrate, bismuth subnitrate, bismuth tartrate, bismuth subcarbonate, bismuth subgallate, bismuth subsalicylate, and tripotassium dicitrato bismuthate, bismuth subgallate, and mixtures thereof. A particularly preferred bismuth salt is bismuth subsalicylate.

A variety of compositions containing bismuth salts are commercially-available, including, for example, DeNol®, containing tripotassium dicitrato bismuthate (sold by Gist-Brocades N.V.), Noralac®, containing bismuth aluminate, alginic acid, and magnesium carbonate (manufactured by North American Pharmaceuticals), Roter bismuth, containing bismuth subnitrate (sold by Roter Laboratories), Fensobar Polvo, containing bismuth subcarbonate among other materials (manufactured by USV Pharmaceutical Corporation), Pepto-Bismol®, containing bismuth subsalicylate (sold by The Procter & Gamble Company) and ranitidine bismuth citrate (Tritec® available from Glaxo Wellcome p.l.c.).

A wide variety of antimicrobials are useful in this invention. As used herein, such "antimicrobials" refer to any naturally-occurring, synthetic or semi-synthetic compound or composition, or mixture thereof, which is safe for human use as used in the packages and methods of this invention, and is effective in killing or substantially inhibiting the growth of *H. pylori* when used in the methods/package of this invention. Antibiotics are among

the preferred antimicrobials useful herein. Such antibiotics can be generally classified by chemical composition, into the following principal groups: the aminoglycosides, such as gentamicin, neomycin, kanamycin, and streptomycin; the macrolides, such as erythromycin, clarithromycin, azithromycin, dirithromycin, troleandomycin, clindamycin, and rifampin; the penicillins, such as penicillin G, penicillin V, ampicillin and amoxicillin; the polypeptides, such as bacitracin and polymyxin; the tetracyclines, such as tetracycline, chlortetracycline, oxytetracycline and doxycycline; the cephalosporins, such as cephalexin and cephalothin; and such miscellaneous antibiotics as chloramphenicol and clindamycin. These antibiotics can be generally said to function in one of four ways: inhibition of cell walls synthesis, alteration of cell wall permeability, inhibition of protein synthesis, or inhibition of nucleic and synthesis.

Other antimicrobials useful herein include the sulfonamides; nitrofurans, such as nitrofurazone nitrofurantoin, and furozolidone; and metronidazole, tinidazole, and nimorazole. Antimicrobials among those useful herein are described in the following publications, incorporated by reference herein: *Remington's Pharmaceuticals Sciences* (15th edition 1975); F.H. Meyers, et al., *Review of Medical Pharmacology* (7th edition 1980); *Gaddum's Pharmacology* (8th edition 1978); and A. Goodman, A.G. Goodman and L.S. Gilman, *The Pharmacological Basis of Therapeutics* (6th edition 1980).

While any of these antimicrobials may be used, penicillin, erythromycin, tetracycline, doxycycline, metronidazole, tinidazole, amoxicillin, ampicillin, clarithromycin, and nitrofurantoin are among the preferred antimicrobials for use in the present invention.

Examples of particularly preferred peroral complex drug regimen include regimens such as: 1) a bismuth salt (e.g., bismuth subsalicylate), metronidazole, and amoxicillin or tetracycline; 2) lansoprazole, amoxicillin, and clarithromycin; 3) ranitidine bismuth citrate (Tritec® available from Glaxo Wellcome p.l.c.); 4) omeprazole and clarithromycin; and 5) ranitidine bismuth citrate and amoxicillin and/or clarithromycin.

Other preferred peroral complex drug regimens are disclosed in U.S. Pat. No. 5,256,684, Marshall, issued Oct. 26, 1993, The Procter & Gamble Co., which is herein incorporated by reference in its entirety.

The specific method of aiding and/or improving patient compliance by administering one or more therapeutically active agent(s), according to the packaging or process of this invention, may depend upon such factors as the particular therapeutic agent used, the site of action desired, the amount of therapeutic agent to be administered per day, the presence or potential of any adverse side effects, and the potential for any interactions between therapeutic agents used. Thus the therapeutic agent(s) can be administered by single daily doses, or be administered in two, three, or four or more doses per day.

Whether two or more therapeutic agents are administered simultaneously, concurrently or sequentially depend on potential interactions between these agents, which are known to those skilled in the art.

The Blister Card

The compliance package of the present invention comprises at least one blister card. Each blister blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient. The blister card is divided into sections, preferably perforated sections, separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time in which the dose is to be administered, i.e. "Breakfast," "Lunch," "Dinner," "Bedtime," etc.

Also, preferably if the daily dose of the complex peroral drug regimen varies throughout the course of therapy, the blister cards are arranged in sequential order of administration. For example the blister card can comprise an indicia denoting each separate day of treatment ("Day 1," "Day 2," "Day 3", or "Monday," "Tuesday," "Wednesday," etc.) or an indicia denoting the order that each separate blister card is to be administered ("1," "2," "3," or "Card 1," "Card 2," "Card 3," etc.) Preferably for these varying dosage regimens, the first card to be used will be placed at the beginning of the blister card stack in the compliance package container.

Preferably the blister card and/or compliance package is child resistant and/or tamper evident, which, while providing easy access to the end user, has child-resistant features.

Child resistant blister packages are disclosed in U.S. Pat. No. 3,809,221, Compere, issued May 7, 1974; U.S. Pat. No. 4,398,634, McClosky, issued Aug. 16, 1983, Wrapade Machine Company, Inc.; U.S. Pat. No. 3,809,220, Arcudi, issued May 7, 1974, Becton Dickinson and Company; U.S. Pat. No. 3,503,493, Nagy, issued March 31, 1970; U.S. Pat. No. 3,924,746, Haines, issued December 9, 1975, Paco Packaging; U.S. Pat. No. 4,011,949, Braber, et al., issued March 15, 1977, The Lehigh Press; U.S. Pat. No. 3,924,747, Gerner, issued Dec. 9, 1975, Packaging Coordinators, Inc.; U.S. Pat. No. 4,537,312, Intini, issued Aug. 27, 1985. All of the above references are incorporated herein by reference, in their entirety.

Preferably the following information is printed on the blister card:

1. Preferably each dose is labeled with the time of day that the dose is to be administered, for example, "Breakfast," "Lunch," "Dinner," and "Bedtime." This is to help patients take the medication at the correct times. In addition this will help the patients to recognize when and if they have missed a dose.

2. Preferably if the daily dose of the complex peroral drug regimen varies throughout the course of therapy, the blister cards are arranged in sequential order of administration. Therefore, preferably each blister card comprises an indicia denoting the order that each separate blister card is to be administered. For example the blister card can be optionally marked with "Day 1," "Day 2," "Day 3", or "1," "2," "3," or "Card 1," "Card 2," "Card 3," etc.

3. The names of the therapeutic agent or agents and the doses contained in the blister card and dose section of the blister card.

Each blister card of the present invention contains a full daily dose of the peroral complex drug regimen. Therefore, the patient can carry a 1-day supply with them during the day, in either their purse or pocket, etc. Preferably the blister card is approximately 3.75 X 4.75 inches or is a size that a single card will fit into a standard size shirt pocket. If the blister card is larger, it can be folded in half to reduce its dimension so than it will easily fit into a purse, pocket, etc., if necessary.

In addition one preferred embodiment of the present invention is a compliance package or kit also comprising a separate cover or case to hold a single-blister card. This case will protect the blister card from damage. In addition this case is another way for the patient to transport the blister card during the day so that the doses of the complex drug regimen are readily accessible to patient.

In another embodiment of the present invention, this blister card cover or case will also comprise an alarm as the reminder aid. Therefore, the patient can set the alarm to sound when the next scheduled dose is to be administered by the patient.

The portability of the single blister cards eliminates the need for the patient to carry the entire kit or compliance package. It also eliminates the need to transfer the complex drug regimen to another unlabeled vial or container. The transportability of the single blister cards allows the patient to have the dose at hand when the patient is away from home.

Preferably, the single dose sections on the blister cards are arranged in order of the time of administration intervals. For example if the peroral drug regimen comprises 4 daily doses of one or more therapeutic agent(s), then the blister card will preferably comprise four does sections, preferably of equal dimensions, and preferably separated by perforations.

If the peroral complex drug regimen has more than one therapeutic agent to be given as part of the same dose of the regimen, preferably the blister card has only one medication per blister cavity. However these units of medication will be located in the same dose section of the blister card. This will avoid any potential physical interactions between two or more different therapeutic agents.

The blister cards provide positive (or negative) feedback to the patient or physician since they can look at the blister cards to see whether all of the doses of the complex peroral drug regimen have been taken by the patient.

Daily Calendar, Patient Information Booklet and Reminder Aid

The compliance package of the present invention additionally comprises the following:

(1) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(2) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(3) preferably a reminder aid selected from the group consisting of:

1) one or more reminder cards comprising information to remind the patient when to take a dose of the complex drug regimen;

2) one or more adhesive stickers comprising information to remind the patient when to take a dose of the complex drug regimen;

3) a case of the size to contain a single blister card, the case comprising an alarm which can be set by the patient to sound at the time that the next dose is to be administered; and

4) combinations thereof.

"Information" as used herein includes, but is not limited to, anticipated benefits of the therapy with the peroral complex drug regimen, the importance of complying with the dosage and administration instructions, side effect information, the point in time during therapy that side effects occur, dosage information, and information regarding the disease or condition being treated.

The multiple components of the compliance package of the present invention are critical in that they provide repetition of the information (dosing information, side effect information, disease information, and patient incentive information) to the patient. This is to ensure that the patient remembers the information and is sufficiently motivated to complete the full course of treatment. In addition the multiple components, such as the booklet, calendar, indicia and other printed information on the blister cards, reminder aids. etc. provides a continuous source of information to the patient. Preferably, the side effect information, dosing information, disease information, and patient incentive information is repeated at least two times, more preferably at least 3 times in the compliance package.

As used herein "information, dosing information, side effect information, information describing the disease being treated and patient incentive information" means

educational information that the patient is able to understand and use. Preferably the this information is written at a low readability level, i.e. is written such that the average patient or consumer can understand the information. Complex and difficult medical terminology should be translated into more simple words. The readability level of the patient information is very important since it has been reported that patients do not understand many medical terms used in patient information materials. D.L. Smith, Compliance Packaging: A Patient Education Tool, *Amer Pharm,* Vol. NS29, No. 2, p. 42-53,1989.

Preferably this information also includes graphics and illustrations for providing further repetition and reinforcement of the written information.

The side effect information should not only list the possible side effects but should be complete enough to allow the patient to manage side effects. For example, the statement "bismuth may darken the stool or tongue but this darkening will go away after the therapy is complete," helps the patient manage this side effect. Also, the side effect information can instruct the patient to contact the prescriber if side effects are bothersome to the patient. Furthermore, for medications causing hypersensitivity of the patient's skin to sun exposure, the patient is instructed to avoid the sun and sunlamps as much as possible and to wear a high numbered SPF sunscreen.

Additionally the patient is instructed how and when to made up any missed doses of the medication.

The information of the compliance package and methods of the present invention is preferably not coercive, threatening or demeaning to the patient being treated. Although one can provide the patient with very comprehensive information about the complex drug regimen and the disease or condition being treated, this information will not be effective if the patient is not motivated to use the information and comply with instructions for using and administering the complex drug regimen.

Therefore, the compliance packages and methods of the present invention also comprise "patient incentive information." "Patient incentive information" as used herein means specific written material or instructions which provides cues for appropriate behavior or prompting of the patient to comply with the therapeutic drug regimen. Patient incentive information includes statements providing positive feedback and/or encouragement such as congratulatory statements, statements complementing the patient during various intervals of the complex drug regimen for complying with the regimen, statements that encourage compliance by highlighting the benefits of properly administered medication (i.e. lower chance of side effects, lower chance of the reoccurrence of infection, lower chance of the development of antimicrobial resistance, lower chance of re-treatment, etc.) statements that encourage compliance by highlighting the benefits of completing the therapy (i.e. reduction or elimination of the disease symptoms), statements indicating that

the patient has some control over the treatment and that the patient has chosen to participate in the regimen and is therefore involved in the decision making process concerning the regimen, etc.

Patient incentive information can also inform the patient that compliance with the proper dosage administration may save the patient time and money as well. In particular, patient incentive information can inform the patient that by complying with proper dosing instruction and finishing the full course of complex drug regimen, the patient may reduce the number of trips to his or her physician, decrease the number of medications prescribed due to re-treatment of conditions due to non-compliance and due to recurrence of infections (in the case of antimicrobial non-compliance), etc. Furthermore, complying with the proper dosage regimen may avoid side effects and adverse reaction which could necessitate the need for basic laboratory work, x-rays, ECGs, diagnostic tests, intravenous and parenteral drug therapy and even hospitalization to treat severe complications.

The following exemplifies some specific forms of patient incentive information of the present invention.

1. "The reward for your efforts may mean freedom from your _____ (Specific disease or condition.)"
2. "Stick with it!"
3. "You are now in control."
4. "You are one-third of the way through your therapy!"
5. "Keep up the good work!"
6. "Each day of treatment helps bring freedom from your _____ (Specific disease or condition.)
7. "You are one-half of the way through your therapy!"
8. "Each day of treatment helps bring freedom from your symptoms."
9. "Congratulations! You are halfway through your drug therapy. Just one more week (or number of days, etc.) to go!"
10. "Now you are two-thirds of the way through your therapy."
11. "Just think -- freedom from your _____ (disease or condition) can be on the horizon."
12. "Just think -- freedom from your symptoms can be on the horizon."
13. "Aren't you glad that you've made the effort to take your medicine according to the instructions?"
14. "Each dose of therapy counts."
15. "Freedom from your _____ (disease or condition) can be within your reach."
16. "Freedom from your symptoms can be within your reach."

17. "Don't slack off now -- stick with your scheduled doses through tomorrow -- and take a bow!"

18. "You did it!"

19. "Congratulations!"

20. "Take all of your medicine today and you can look forward to a future free of your _____ (disease or condition.)"

21. "Take all of your medicine today and you can look forward to a future free of your symptoms."

22. "Take charge of your future!"

The calendar of the present invention comprises separate pages corresponding to each day of treatment for the peroral complex drug regimen. Preferably, the calendar is provided so that after the patient takes the daily dosage of the drug regimen, the patient can either tear off a page of the calendar or can cross out that particular page. The calendar can be taken to the patient's next visit to their prescriber to confirm the level of the patient's compliance with the complex drug regimen. The calendar is preferably attached to the inside lid of the compliance package.

Preferably the compliance package comprises a number of reminder cards or adhesive stickers equal to the number of daily doses to be administered by the patient. Preferably the compliance package reminder aid is one or more adhesive stickers.

Preferably each reminder aid (adhesive stickers or reminder card) is provided in a form to allow the patient to place the sticker or card at a location that the patient will be, at the time a dose of the complex drug regimen is due to be taken by the patient. For example, the reminder sticker or card can be placed on the patient's refrigerator, television, alarm clock, computer screen, bathroom mirror, medicine cabinet, desk, dining table, nightstand, coffee pot, toothbrush, etc.

The written instruction on the adhesive sticker or reminder card comprises one or more of the following: the drug trade name, generic name, a statement such as "Don't Forget To Take Your Medication," "Take Your Next Dose at ____," etc.

Also, preferably the blister cards are separated, at approximately one-fourth to three-fourths of the way between the start and the finish of the complex drug regimen, by a card comprising patient information and patient incentive information. This card preferably contains a statement on the importance of completing the full course of drug therapy to avoid disease or symptom reoccurrence. Preferably in compliance packing for the treatment of *H. pylori* infections of the gastrointestinal tract, this card is located approximately between day 3 and day 4 (blister card 3 and 4), day 4 and 5 (blister card 4 and 5), day 5 and 6 (blister card 5 and 6), day 6 and 7 (blister card 6 and 7), or day 7 and 8

(blister card 7 and 8). This is because symptoms generally subside with antimicrobial therapy early in the course of treatment.

Preferably for the treatment of *H. pylori* infections, the card is located between blister card 7 and 8 and comprises a congratulatory statement for finishing approximately half of the full course of the complex drug regimen. Preferably for *H. pylori* infections, this card comprises the statement:

> "Freedom from ulcers is on the horizon! Congratulations. You've finished the first 7 days of your 14-day treatment. You may feel better, but be sure to keep taking your medicine. You need all 14 days of medicine to kill the germs that cause the ulcer. If you stop now, some germs may not be dead and your ulcer could return. So keep up the good work! Don't stop until all your medicine is gone."

The following are non-limiting examples of the package of this invention.

Example 1

A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) at least one blister card,

wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into sections separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time of day in which the dose is to be administered;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

wherein the complex drug regimen comprises varying the dosage level or the dosage interval for a single therapeutic agent, the simultaneous administration of more than one therapeutic agent, the concurrent administration of more than one therapeutic agent.

Example 2

A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) at least one blister card,

wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into sections separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time of day in which the dose is to be administered;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) a reminder aid selected from the group consisting of:

1) one or more reminder cards comprising information to remind the patient when to take a dose of the complex drug regimen;

2) one or more adhesive stickers comprising information to remind the patient when to take a dose of the complex drug regimen;

3) a case of the size to contain a single blister card, the case comprising an alarm which can be set by the patient to sound at the time that the next dose is to be administered; and

4) combinations thereof.

Example 3

A pharmaceutical compliance package, comprising:

(a) a series of 14 blister cards,

wherein each blister card comprises 4 doses of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into 4 perforated sections separating each dose; wherein each dose section comprises a "Breakfast," "Lunch," "Dinner," and "Bedtime" indicia denoting the time in which the dose is to be administered; wherein each dose comprises a bismuth salt, tetracycline and metronidazole, preferably each dose comprises two bismuth subsalicylate tablets with 102 mg of salicylate, one 500 mg tetracycline HCl capsule, and one 250 mg metronidazole tablet; wherein each blister card has only one medication per blister cavity; and wherein preferably the blister cards are separated between the 7th and 8th blister card, by a card containing a statement on the importance of completing the full course of drug therapy to avoid disease/symptom

reoccurrence and a congratulatory statement to the patient for finishing half of the complex drug regimen;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) a reminder aid comprising 4 reminder cards or 4 adhesive stickers, to be placed at the location that the patient will be at the time of each scheduled dose, comprising information to remind the patient when to take a dose of the complex drug regimen.

WHAT IS CLAIMED IS:

1. A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a)at least one blister card, preferably which is child resistant,
wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered by the patient; wherein the blister card is divided into sections separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time of day in which the dose is to be administered;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

wherein the complex drug regimen comprises varying the dosage level or the dosage interval for a single therapeutic agent, the simultaneous administration of more than one therapeutic agent, or the concurrent administration of more than one therapeutic agent.

2. A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) at least one blister card, preferably which is child resistant,
wherein each blister card comprises the total daily dose of the peroral complex drug regimen to be administered; wherein the blister card is divided into sections separating each complex drug regimen dose; wherein each dose section comprises an indicia denoting the time of day in which the dose is to be administered;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) a reminder aid selected from the group consisting of:

1) one or more reminder cards comprising information to remind the patient when to take a dose of the complex drug regimen;

2) one or more adhesive stickers comprising information to remind the patient when to take a dose of the complex drug regimen;

3) a case of the size to contain a single blister card, the case comprising an alarm which can be set by the patient to sound at the time that the next dose is to be administered; and

4) combinations thereof.

3. A pharmaceutical package for aiding or increasing patient compliance for the administration of a peroral complex pharmaceutical drug regimen, comprising:

(a) a series of 14 blister cards, preferably which is child resistant, wherein each blister card comprises 4 doses of the peroral complex drug regimen to be administered; wherein each blister card is divided into 4 perforated sections separating each dose; wherein each dose section comprises a "Breakfast," "Lunch," "Dinner," and "Bedtime" indicia denoting the time in which the dose is to be administered;

(b) a patient information booklet comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information;

(c) a daily calendar comprising dosing information, side effect information, information describing the disease being treated, and patient incentive information; and

(d) a reminder aid comprising 4 adhesive stickers, to be placed at the location that the patient will be at the time of each scheduled dose, comprising information to remind the patient when to take a dose of the complex drug regimen;

wherein the complex drug regimen comprises the simultaneous administration of bismuth subsalicylate, tetracycline, and metronidazole.

4. The compliance package of claim 1, 2 or 3 wherein the patient incentive information comprises statements that the patient has some control over the treatment.

5. The compliance package of claim 1 or 2 wherein the complex drug regimen comprises the simultaneous administration at least one antimicrobial agent and bismuth.

6. The compliance package of claim 1 or 2 wherein the complex drug regimen comprises the simultaneous administration of at least one antimicrobial agent and a proton pump inhibitor.

7. The compliance package of claim 2 wherein each blister card comprises an indicia denoting the order that each separate blister card is to be administered for complex drug regimens which are to be administered sequentially or which the dosage level or the dosage interval for a single therapeutic agent varies from day to day, wherein preferably the indicia comprises each separate day of treatment.

8. The compliance package of claim 2 wherein, half way through the drug regimen, the blister cards are separated by a card containing patient information and patient incentive information.

9. The compliance package of claim 3 wherein the blister cards are separated between the 7th and 8th blister card, by a card comprising patient information and patient incentive information on the importance of completing the full course of drug therapy to avoid disease or symptom reoccurrence.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 97/20577

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61J7/04 B65D75/54

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61J B65D

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 43 24 771 A (GEBHARDT KARL MARTIN) 18 August 1994 see abstract	1,2,4,7
Y	see column 5, line 52 - column 6, line 8; figure 1	8
X	US 4 553 670 A (COLLENS RICHARD) 19 November 1985 see the whole document	1
X	US 3 780 856 A (BRAVERMAN M) 25 December 1973 see figures 1,2	1
P,X	WO 97 03896 A (ELI LILLY JAPAN KABUSHIKI KAIS ;UWATOKU KEIKO (JP)) 6 February 1997 see abstract; figures	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of theinternational search	Date of mailing of the international search report
20 February 1998	02/03/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Godot, T

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INTERNATIONAL SEARCH REPORT

In. .ational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DE 31 39 403 A (KLOCKE HARTMUT) 14 April 1983 see the whole document	1
A	US 4 811 845 A (BAGGETT JOBETH) 14 March 1989 see column 4, line 57 - column 5, line 5; figure 2	1,2
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A	US 4 189 053 A (ANTOSIK WALTER ET AL) 19 February 1980 see abstract; figures	3,8,9
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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